COEURative

Creating Curative Strategies for Cardiovascular Diseases Related to Cellular Hypoxia

An Introduction

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Founder, President and CEO

Cardiovascular Opportunity and COVID-19

- Nitric Oxide (NO) is donated by Nitroglycerin to relax blood vessels where the lining of the blood vessel has been injured.
- Novel compounds created to donate NO were developed by binding a urea-like molecule onto the generic agent isosorbide mononitrate, a well-known NO donor, to combat vascular endothelial dysfunction more effectively. Urea facilitates cellular NO synthesis.
- Inflammation is a key contributor to cardiovascular diseases. Pharmaceutical inhibition of vascular inflammation remains the future of cardiovascular medicine. NO is believed to be a part of this process in hypoxic blood vessels and NO also has antiviral activity.
- These NO producing compounds developed for cardiovascular medicine should also combat vascular endothelial dysfunction in COVID-19, a disease characterized by systemic hypoxia and inflammation due to COVID-19 virus infection.

What Is Hypoxia?

Hypoxia is a deficiency of oxygen at the cellular level that triggers expression of specific phenotypes (patterns of gene expression and cell function) that lead to changes in almost every aspect of cell biology.

- Hypoxia leads to expression of genes in blood vessel lining cells that regulate inflammation and ischemic preconditioning (protecting against myocardial infarction) while reducing expression of the gene for endothelial nitric oxide synthase, changing the dilatation of blood vessels.
    - Schmedtje et al., J. Biol. Chem. 1997;272:601-608.

COVID-19

- COVID-19 pneumonitis and myocarditis creates hypoxia. Death is ultimately due to systemic oxygen deprivation.
- Myocardial injury has a significant association with a fatal outcome in COVID-19. Cardiac troponin is the biomarker.
    - Guo et al., JAMA Cardiol. March 27, 2020. doi:10.1001/jamacardio.2020.1017
- Nitric oxide donor compounds can inhibit SARS-coronavirus infection *in vitro*.
    - Keyaerts et al., Int. J. Infect. Dis. 2004; 8:223-226.
- Strategies to manage this problem should include vasodilatation in the setting of oxygen deprivation and modulation of inflammatory responses with NO. The proprietary compounds of Coeurative, Inc. should also directly inhibit the COVID-19 virus via specific binding to protein receptors.
    - Coeurative, Inc., Patents pending, filed in March and June, 2020.

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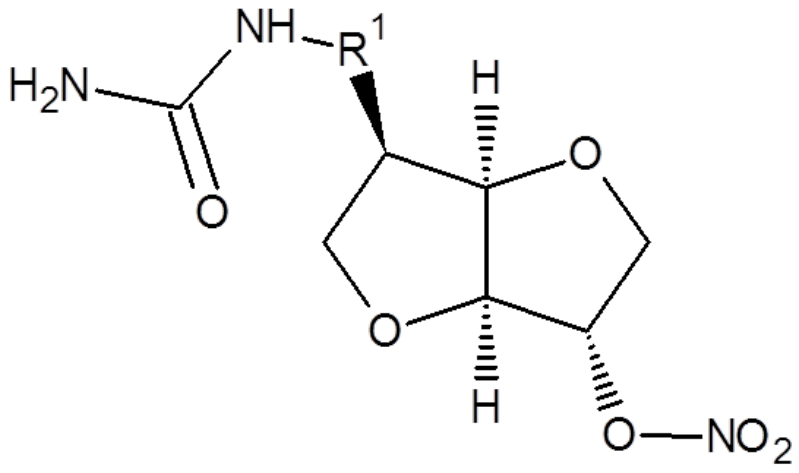
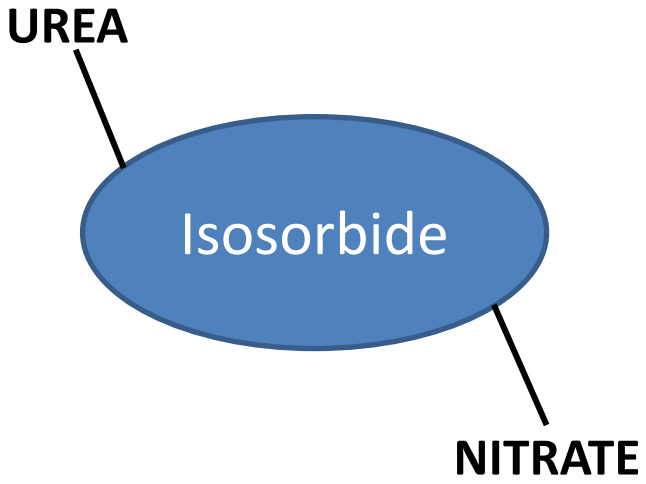
Novel Therapeutics From Coeurative, Inc.





- **The proprietary compounds are novel variants of a generic drug, isosorbide mononitrate, with an attached urea moiety or urea analogue.**
- **These compounds will donate a nitrate group to increase vascular nitric oxide (NO) while increasing net endothelial urea.**
- **Arginine is metabolized to form urea via the enzyme arginase. If urea is in oversupply, arginine will be metabolized instead into NO via endothelial nitric oxide synthase.**
- **NO is formed from both arginine and nitrate via a dual pathway with a "one-two-punch."**

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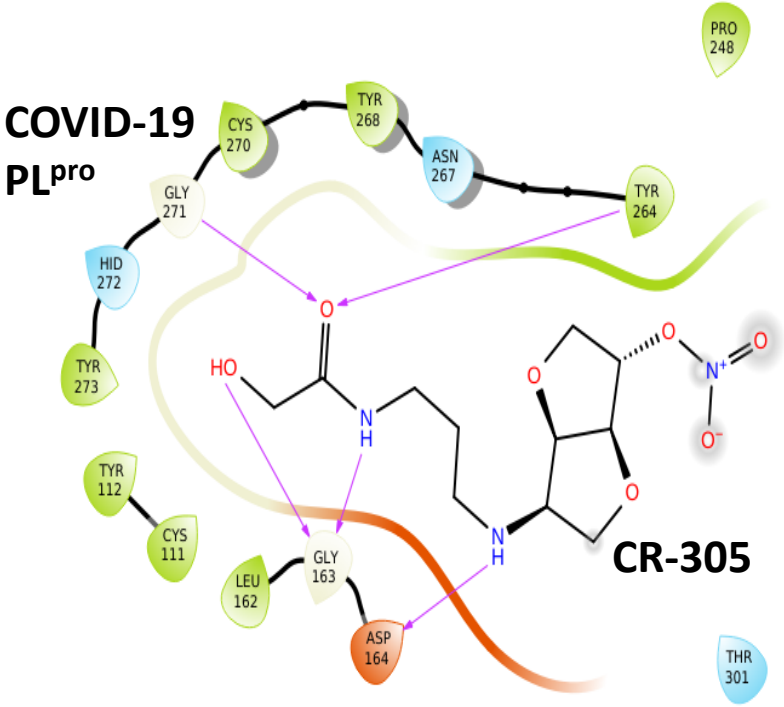
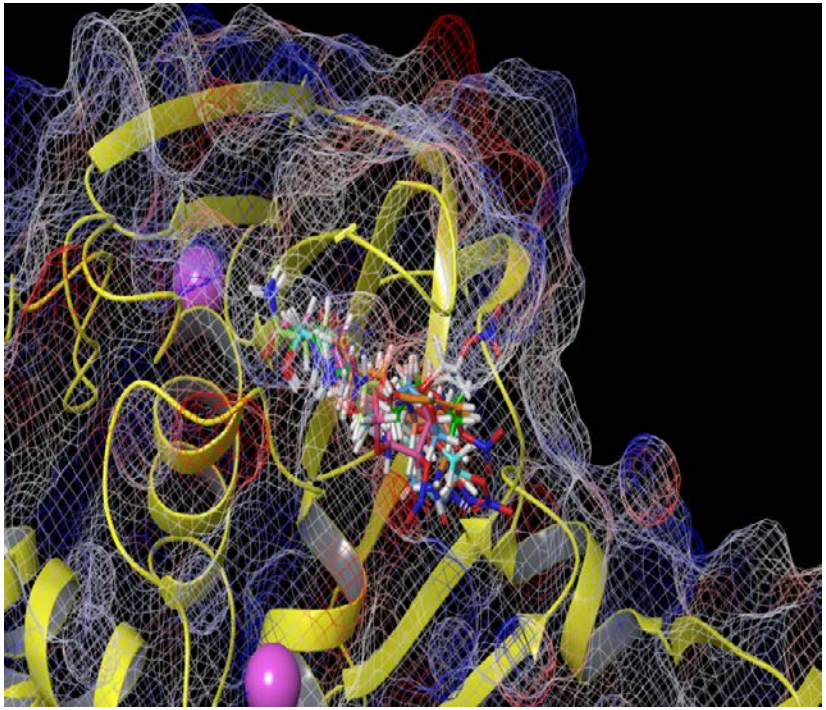
Novel Therapeutics and Indications

- Patent no. US 10,501,471 awarded December, 2019.
  - Continuation and PCT patent applications pending.
- Proof of mechanism studies are underway. There are three proposed indications for these compounds.
  - The first indication is as an antianginal agent. The compounds are expected to improve exercise capacity in the setting of local hypoxia and coronary artery disease with the drugs acting as coronary vasodilators through augmented release of endothelial nitric oxide.
  - The second indication is for secondary prevention of major adverse events associated with endothelial hypoxia in cardiovascular diseases. Vasodilatation is sought as well as ischemic preconditioning and modulation of vascular inflammatory mediators via the augmented release of endothelial nitric oxide.
  - The third and latest indication is as an anti-viral agent with particular effect on COVID-19 virus (SARS-CoV-2.) Direct anti-viral activity is expected from these NO donors as well as benefits related to the first two indications in these patients.

CR-305 Delivers Nitric Oxide to COVID-19 Virus

- Based on the generated docking model, CR-305 is bound in the active site of the COVID-19 surface PL^{pro} enzyme, similar to Ribavirin.
- The interaction with the enzyme suggests the potent inhibitory effect of this compound against the COVID-19 virus.
- PL^{pro} is considered to be a primary target for therapeutic inhibition of the COVID-19 virus.





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COEURATIVE: Drug Development Strategy

- Patent no. US 10,501,471 awarded December, 2019.
  - Continuation and PCT patent applications pending.
- Coeurative, Inc. is raising $1M in a Series Seed raise to support work refining its proprietary small molecules in *ex vivo* proof of mechanism studies for human therapeutic applications.
- $100,000 of the $1M raised by the end of 2019.
- Subsequent Series A and B raises with preclinical studies will be followed by licensing rights to big pharma, after filing of IND, under a 5-Year Development Plan.
- Completion of the NDA with the FDA after another 5 years of clinical trials.

COEURATIVE: Five Year Development Plan

- Drug synthesis in collaboration with Cayman Chemical.
- Human cell culture *ex vivo* in Biospherix incubator facility at Coeurative's Roanoke lab for "drug development in a dish."
  - Assay gene expression, protein prevalence, markers of function and toxicity.
  - Measure cellular release of Nitric Oxide and Reactive Oxygen Species.
  - Use human cardiovascular cells commercially available and BOEC (Blood Origin Endothelial Cells) derived from patients with cardiovascular diseases.
- Measure antiviral activity with direct testing (UTMB-Galveston.)
- Select drug(s) for *in vivo* animal studies of safety/toxicity and ADME (absorption, distribution, metabolism and excretion) followed by scaled-up synthesis and formulation.
- Investigational New Drug application is made to the FDA.

COEURATIVE: The Founder

- MD, 1981: Graduate of Honors Program in Medical Education at Northwestern University
- MPH, 1983: Harvard School of Public Health
- Internal Medicine Residency, 1986: Baylor College of Medicine
- Cardiology Fellow, 1991: Medical College of Virginia
- Faculty appointments at Baylor, University of Texas Medical Branch, Wake Forest University School of Medicine
- Published on hypoxia in medical science journals with high impact factors such as Circulation Research and Journal of Biological Chemistry
- Winner of the 1996 Cournand & Comroe Young Investigator Prize from the American Heart Association for cardiopulmonary research.
- Team player with a thirty year track record of collaboration with the pharmaceutical industry on clinical trials and drug development.

COEURATIVE, Inc. is creating curative strategies for cardiovascular diseases related to cellular hypoxia.

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